UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/732,411	12/07/2000	Samy Ashkar	CMZ-124CP	1508

23579 7590 01/08/2004

PATREA L. PABST
HOLLAND & KNIGHT LLP
SUITE 2000, ONE ATLANTIC CENTER
1201 WEST PEACHTREE STREET, N.E.
ATLANTA, GA 30309-3400

EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/732,411	ASHKAR, SAMY	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *09/22/2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7,11 and 16-19* is/are pending in the application.

4a) Of the above claim(s) *11 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/22/2003 has been entered.

2. Claims 1, 3-5,7, 11 and 16-19 are pending.

3. Claims 11 and 19 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention because Amended claims 11 and 19 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Amended claims 11 and 19 now recited the use of non-elected SEQ ID NOs: 7 and 14 and 12.

4. Claims 1, 3-5,7 and 16-18 are under examination as they read on a method of inhibiting/decreasing adhesion of a target cell to a substrate comprising providding the target cell with the adhesion modulatory peptided associated substrate of SEQ ID NO:15 (inhibits VLA-4/VCAM interaction) such that adhesion of the target cell to the substrate is inhibited wherein the target cell is endothelial cells, neutrophil and macrophage and wherein the substrate is titanium, a polyvinyl surface, a gel, collagen, hyaluronic acid and PGA.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 4 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 4 is indefinite in the citation of "wherein the integrin is selected from the group consisting of an $\alpha 4\beta 1$ integrin and a VCAM" because vascular cell adhesion molecule (VCAM) is not an integrin molecule. VCAM contains six or seven immunoglobulin domains and is an endothelial ligand for $\alpha 4\beta 1$ integrin. Further it is unclear if applicant meant VCAM-1 or VCAM-2.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 3-5, 7, 16 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "less than about 25000 Daltons" claimed in claim 1, represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 9/22/03 points to the specification at page 19, line 21 to page 20, line 18 for support for the newly added limitations "less than about 25000 Daltons" as claimed in claim 1. However, the specification does not provide a clear support of "less than about 25000 Daltons". The instant claims now recite a limitation which was not clearly disclosed in the specification and recited in the claims as originally filed.

9. Claims 1, 3-5,7 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting binding of VCAM-1 containing cell to $\alpha 4\beta 1$ integrin containing cell *in vitro*, with the adhesion peptide SEQ ID NO: 15, does not reasonably provide **enablement** for a method for inhibiting binding of any cell to any integrin or glycosaminoglycan, comprising providing the cell with a peptide, wherein the peptide has a molecular weight less than about 2500 Daltons and comprises a sequence of SEQ ID NOs: 6, 7, 8, 10, 12, 14, or 15 in claim 1, wherein the cell is within a "subject" in claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim

The specification does not provide a sufficient enabling description of the claimed invention.

The specification discloses the amino acid sequences (SEQ ID NO:1-5 and SDV) with a various functional activity (e.g., pages 9-10, table II). The specification discloses that SEQ ID NO:15 is involve in the inhibition of VLA-4/VCAM interaction.

The term "comprises" in base claim 1 is open-ended. It would expand SEQ ID NO:15 to include additional non disclosed amino acids on either or both sides of the N- and C- terminal of the peptide. A person of skill in the art would not know what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for inhibiting VLA-4/ICAM-1 interaction. Without detailed direction as to which amino acid sequences are essential to the function of the peptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of amino acid sequences encompassed by the instant claims would share the ability to inhibit VLA4/VCAM-1 interaction of the peptide of SEQ ID NO:15, other than the amino acid of SEQ ID NO:15.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of peptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a peptide's amino acid sequence and still retain similar biological activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly in tolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to tits function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain function aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

In support, Kogan et al. ((J. Biol. Chem.,1995) disclose that single amino acid can determine the ligand specificity of a selectin and the unpredictable nature of amino acid alterations in adhesion/binding activity (see entire document, including the Discussion).

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the method of inhibiting adhesion indices adhesion inhibitory peptide such as adhesion-based molecules can be species – and model-dependent, it is not clear that reliance on the peptide of SEQ ID NO: 15 that inhibits Vla-4/VCAM interaction (page 10, Table II of the instant specification) accurately reflects the relative efficacy of the claimed "functional inhibition" in a subject.

On the basis of the disclosed apparent in vitro observation alone, applicant concludes that the scope of the peptides defined by sequences encompassed by the claimed invention can have biological activity to inhibit the adhesion of target cell to the substrate and be provided as pharmaceutical compositions to subjects including human to effectively inhibit adhesion.

Peptide therapies are unpredictable for the following reasons: (1) the peptide may be inactivated before producing an effect, i.e., such as proteolytic degradation, immunological inactivation or due to and inherently short half-life of the peptide; (2) the peptide may not reach the target area because, i.e., the peptide may not be able to cross the mucosal or the peptide may be adsorbed by fluids, cells and tissues where the peptide has no effect; and (3) other functional properties, known or unknown, may make the peptide unsuitable for in vivo therapeutic use,. i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992)

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 9/22/03, have been fully considered, but have not been found convincing.

Applicant assets that each peptide is specifically demonstrated to inhibit binding, and appropriate cell types and ligands specifically identified- See page 19, line 21, to page 20. line 18. Futher, Applicant asserts that secondary effects of the claimed peptides, if any (i.e. production of cytokines), have nothing to do with the claimed methods. It is well established there it is not enough for the Examiner just to assert that the claims are not enabled. He must provide some evidence for why one skilled in the art would not think it was not enabled. Applicant contends that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.

This is not found persuasive because no common structural basis for the common functionality of disclosed peptides species is provided. Further, the specification does not disclose any methods or working examples that demonstrate that the peptide of SEQ ID NO: 15 or even any other peptide of the instant application exhibit the claimed activities of inhibiting VLA-4/VCAM-1 interaction. The skilled artisan would not reasonably expect a peptide having SEQ ID NO: 15 to function in a subject based sole on in vitro observation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the peptide sequence of SEQ ID NO:15. While experimental testing techniques using cell surface receptor binding compounds are available, it is not routine in the art to use such methods when the expectation of success is unpredictable based on the instant disclosure. Thus, it would require an undue amount of experimentation of one skilled in the art to practice the invention as broadly claimed.

While the specification identifies some broad categories of peptides that might work, these descriptions, without more precise guidelines amount to little more than, "a starting point, a direction for further research." *Genentec, Inc. V. Novo Nordisk* A/S, 108 F.3d 1361, 1366, 42 U.S. PQ.2d (BNA) 1001, 1005 (Fed. Cir. 1997).

10. Claims 1, 3-5, 7 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of inhibiting binding of VCAM-1 containing cell to $\alpha 4\beta 1$ integrin containing cell *in vitro*, with the adhesion peptide SEQ ID NO: 15.

Applicant is not in possession of a method for inhibiting binding of any cell to any integrin or glycosaminoglycan, comprising providing the cell with a peptide, wherein the peptide has a molecular weight less than about 2500 Daltons and comprises a sequence of SEQ ID NOs: 6, 7, 8, 10, 12, 14, or 15 in claim 1, wherein the cell is within a "subject" in claim 17.

Applicant has disclosed only peptides of SEQ ID NO: 1-15 and SDV; therefore, the skilled artisan cannot envision all the contemplated peptide sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant's arguments, filed 9/22/03, have been fully considered, but have not been found convincing.

Applicant traverse the rejection to the extent that it is applied to the amended claims. Applicant asserts that the claims define specific peptides. Applicant further asserts that the specification provides thes sequences and demonstrate that each peptide has been shown to prevent binding of a cell to an integrin or glycosaminoglycan. Applicant contends that there can be no issure about whether or not the applicants has possession of claimed subject matter.

Contrary to Applicant assertions the specification only disclosed SEQ ID NO:15 that inhibits VLA-4/VCAM-1 interaction. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of peptide comprising the peptide of SEQ ID NO:15, which specifically inhibits VLA-4/VCAM-1 interaction.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
January 5, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600